PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 May 2001 (09.05.01)	
International application No. PCT/US00/15410	**Applicant's or agent's file reference** P01899WO0
International filing date (day/month/year) 01 June 2000 (01.06.00)	**Priority date** (day/month/year) 01 June 1999 (01.06.99)
Applicant ZOGHBI, Huda, Y. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 December 2000 (29.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

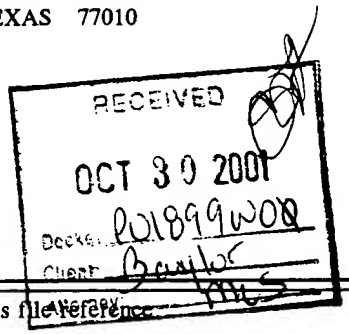
The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992) US0015410

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: THOMAS D. PAUL
FULBRIGHT & JAWORSKI
1301 MCKINNEY, SUITE 5100
HOUSTON, TEXAS 77010



PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	25 OCT 2001
Applicant's or agent's file reference: P01899WO0	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US00/15410	01 JUNE 2000	01 JUNE 1999

Applicant
BAYLOR COLLEGE OF MEDICINE

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL C. WILSON Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992) ★

PATENT COOPERATION TREATY

Received
DEC 0 8 2000 us2
Docket: P01899WO0
Client: BAYLOR
Attorney: MLS.

From the INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS D. PAUL
FULBRIGHT & JAWORSKI
1301 MCKINNEY, SUITE 5100
HOUSTON, TEXAS 77010

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing *(day/month/year)* 04 DEC 2000
Applicant's or agent's file reference P01899WO0	**FOR FURTHER ACTION** **See paragraphs 1 and 4 below**
International application No. PCT/US00/15410	International filing date *(day/month/year)* 01 JUNE 2000
Applicant BAYLOR COLLEGE OF MEDICINE	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later) .

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JANET M. KERR
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/ISA/220 (July 1998) ★

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P01899WO0	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US00/15410	International filing date *(day/month/year)* 01 JUNE 2000	(Earliest) Priority Date *(day/month/year)* 01 JUNE 1999
Applicant BAYLOR COLLEGE OF MEDICINE		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   [ ] contained in the international application in written form.
   [ ] filed together with the international application in computer readable form.
   [X] furnished subsequently to this Authority in written form.
   [X] furnished subsequently to this Authority in computer readable form.
   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has b een furnished.
2. [ ] **Certain claims were found unsearchable** (See Box I).
3. [ ] **Unity of invention is lacking** (See Box II).
4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established by this Authority to read as follows:
   The Title is too long. See PCT Rule 4.3
   New Title: Composition and Methods for the Therapeutic Use of an Atonal-Associated Sequence.
5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is Figure No. _____
   [ ] as suggested by the applicant.
   [ ] because the applicant failed to suggest a figure.
   [ ] because this figure better characterizes the invention.
   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15410

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/320.1, 455, 456, 458; 514/2, 44; 530/350; 536/23.1, 23.5, 24.1; 800/3, 9, 13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	BEN-ARIE. N. et al. Abnormal Cerebellar Development in Mice Lacking the Murine Homolog of the Drosophila Proneural Gene Atonal. American J. Human Genetics. 1996. Vol. 59. No. 4. Suppl. page A46, Abstract #232, see abstract.	1, 3, 5, 6, 10 ---- 11-17
X ---- Y	BEN-ARIE.N. et al. Math1 is Essential for Genesis of Cerebellar Granule Neurons. Nature. 13 November 1997. Vol. 390. pages 169-172, see the entire document.	1-10 ---- 11-17
X --- Y	SUN.Y. et al. Transcriptional Regulation of Atonal During Development of the Drosophila Peripheral Nervous System. Development. 1998. Vol. 125. pages 3731-3740, especially pages 3732, under DNA constructs, and pages 3733-3734, under Results.	40-43 ---- 46

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 19 OCTOBER 2000	Date of mailing of the international search report 04 DEC 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JANET M. KERR Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998) ★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15410

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SABATE.O. et al. Adenovirus for Neurodegenerative Diseases: In Vivo Strategies and Ex Vivo Gene Therapy Using Human Neural Progenitors. Clinical Neuroscience. 1996. Vol. 3. pages 317-321, especially page 317, right column, and page 318, left column.	18-39
Y	WILLIAMS.D.P. et al. Structure/Function Analysis of Interleukin-2-Toxin (DAB486-IL-2), Fragment B Sequences Required for the Delivery of Fragment A to the Cytosol of Target Cells. J. Biol. Chem. 15 July 1990, Vol. 265. No. 20. pages 11885-11887, see entire document.	44, 45
X	CHIEN.C.-T. et al. Neuronal Type Information Encoded in the Basic-Helix-Loop-Helix Domain of Proneural Genes. Proc. Natl. Acad. Sci. USA. November 1996. Vol. 93. pages 13239-13244, especially pages 13239-13240.	1, 10
Y,P	SCHWARZE. S.R. et al. In Vivo Protein Transduction: Delivery of a Biologically Active Protein into the Mouse. Science. 03 September 1999. Vol. 285, pages 1569-1572, see entire document.	46
A	VERMA. I.M. et al. Gene Therapy-Promises, Problems and Prospects. Nature. 18 September 1997. Vol. 389. pages 239-242, see entire document.	18-39
A	Ledley. F.D. Pharmaceutical Approach to Somatic Gene Therapy. Pharmaceutical Research. November 1996. Vol. 13. No. 11. pages 1595-1614, see entire document.	18-39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15410

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K 38/00; C07H 21/04; C07K 14/00, 14/46, 14/435; G01N 33/00; C12N 15/00, 15/09, 15/12, 15/63, 15/67, 15/85, 15/86, 15/87, 15/86

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/320.1, 455, 456, 458; 514/2, 44; 530/350; 536/23.1, 23.5, 24.1; 800/3, 9, 13

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS, WEST, STIC SEQUENCE SEARCH:
search terms: Seq ID No. 58, math1, math2, hath1, hath2, atonal, ato, atonal-associated, amino acid sequence, nucleic acid sequence, polynucleotide, transgene, treatment, administration, delivery, receptor binding domain, bacterial toxin, zoghbi huda, bellen hugo, bermingham nessan, hassan bassem, ben-arie nissim

09/980,381

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P01899WO0	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/15410	International filing date *(day/month/year)* 01 JUNE 2000	Priority date *(day/month/year)* 01 JUNE 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant BAYLOR COLLEGE OF MEDICINE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   I [X] Basis of the report

   II [ ] Priority

   III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV [ ] Lack of unity of invention

   V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI [ ] Certain documents cited

   VII [ ] Certain defects in the international application

   VIII [X] Certain observations on the international application

CORRECTED VERSION

Date of submission of the demand	Date of completion of this report
29 DECEMBER 2000	26 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Della Collins for MICHAEL C. WILSON Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/15410

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages (See Attached) , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the drawings:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	2, 4, 8, 9, and 11-55	YES
	Claims	1, 3, 5-7, 10	NO
Inventive Step (IS)	Claims	2, 4, 8, 9, and 11-55	YES
	Claims	1, 3, 5-7, 10	NO
Industrial Applicability (IA)	Claims	1-55	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1, 3, 5-7, and 10 lack novelty under PCT Article 33(2) as being anticipated by Ben-Arie et al. (Nature).

Ben-Arie et al. teach transgenic mice lacking one or both alleles of an atonal-associated nucleic acid sequence (MATH 1). The transgenic mice were generated by homologous recombination protocols using a vector comprising a nucleic acid sequence encoding a reporter gene flanked by an atonal-associated nucleic acid sequence. The mice lack the external germinal layer and lack foliation of the cerebellum. In addition, the mice have a reduction in cerebellum size.

Claims 2, 4, 8, 9 and 11-55 meet the criteria set out in PCT Article 33(2)-(3) since the prior art does not teach or fairly suggest the claimed invention.

Claims 1-55 meet the criteria set out in PCT Article 33(4), because the transgenic animals are useful in studying the phenotypic effects of alterations in proneural gene expression during development.

---------- NEW CITATIONS ----------

NONE

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to contain an adequate written description of the claimed transgenic animals and compositions. The description is inadequate because: the description fails to provide information regarding vector construct design for generating all of the transgenics, compositions and fusion proteins encompassed in the claims.

Claims 1-55 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because: the description does not provide sufficient guidance to make all of the transgenic animals encompassed in the claims. As such, the description does not provide sufficient guidance to use the transgenic animals in the claimed screening methods. In addition, the description does not provide sufficient guidance to make and use the compositions for the claimed treatment methods as the description does not provide sufficient information with respect to how to target the proteins or nucleic acid sequences to specific cells or tissues, which cells or tissues to target, the level of protein or nucleic acid sequence needed for administration, the level of expression of the nucleic acid sequence required to effect a treatment. Furthermore, the state of the art teaches that providing proteins or nucleic acid sequences to treat disease conditions is unpredictable (see Sabate et al., Ledley, and Verma et al.). Finally, the disclosure does not teach any fusion proteins.

Claims 1-55 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): A61K 38/00; C07H 21/04; C07K 14/00, 14/46, 14/435; G01N 33/00; C12N 15/00, 15/09, 15/12, 15/63, 15/67, 15/85, 15/86, 15/87, 15/88 and US Cl.: 435/320.1, 455, 456, 458; 514/2, 44; 530/350; 536/23.1, 23.5, 24.1; 800/3, 9, 13

1. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-121, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims.
page(s) 122-127, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Page 128 filed with the letter of 28 September 2001.

This report has been drawn on the basis of the drawings,
page(s) 1-14, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

47. A fusion protein comprising an *atonal*-associated amino acid sequence or fragment thereof and a desired amino acid sequence.

48. A nucleic acid sequence encoding the fusion protein of claim 47.

49. A method of delivering an *atonal*-associated amino acid sequence to an animal, wherein the method comprises administering to the animal a nucleic acid sequence encoding an *atonal*-associated amino acid sequence and a nucleic acid sequence encoding an additional therapeutic amino acid sequence.

50. The method of claim 20, wherein the method comprises delivering an *atonal*-associated nucleic acid sequence and a second nucleic acid sequence encoding a non-*atonal*-associated therapeutic agent.

51. The method of claim 21, wherein the method comprises delivering an *atonal*-associated nucleic acid sequence and a second nucleic acid sequence encoding a non-*atonal*-associated therapeutic agent.

52. The method of claim 22, wherein the method comprises delivering an *atonal*-associated nucleic acid sequence and a second nucleic acid sequence encoding a non-*atonal*-associated therapeutic agent.

53. The method of claim 24, wherein the method comprises delivering an *atonal*-associated nucleic acid sequence and a second nucleic acid sequence encoding a non-*atonal*-associated therapeutic agent.

54. The method of claim 26, wherein the method comprises delivering an *atonal*-associated nucleic acid sequence and a second nucleic acid sequence encoding a non-*atonal*-associated therapeutic agent.

55. The composition of claim 40, wherein the composition further comprises an additional amino acid sequence or nucleic acid sequence that is not an *atonal*-associated nucleic acid sequence or amino acid sequence.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/73764 A2

(51) International Patent Classification[7]: G01N

(21) International Application Number: PCT/US00/15410

(22) International Filing Date: 1 June 2000 (01.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/137,060	1 June 1999 (01.06.1999)	US
60/176,993	19 January 2000 (19.01.2000)	US

(71) Applicant *(for all designated States except US)*: **BAYLOR COLLEGE OF MEDICINE** [US/US]; One Baylor Plaza, Houston, TX 77030 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZOGHBI, Huda, Y.** [US/US]; 6618 Sewanee, Houston, TX 77005 (US). **BELLEN, Hugo** [US/US]; 3411 Mt. Vernon, Houston, TX 77006 (US). **BIRMINGHAM, Nessan** [US/US]; 5445 Braesvalley #708, Houston, TX 77096 (US). **HASSAN, Bassem** [US/US]; 1422 Richmond Avenue #3053, Houston, TX 77006 (US). **BEN-ARIE, Nissim** [IL/IL]; Department of Cell and Animal Biology, Alexander Silberman Institute of Life Sciences, Hebrew University of Jerusalem, Givat-Ram, 91904 Jerusalem (IL).

(74) Agent: **PAUL, Thomas, D.**; Fulbright & Jaworski, Suite 5100, 1301 McKinney, Houston, TX 77010 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/73764 A2

(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPEUTIC USE OF AN *ATONAL*-ASSOCIATED SEQUENCE FOR DEAFNESS, OSTEOARTHRITIS, AND ABNORMAL CELL PROLIFERATION

(57) Abstract: Compositions and methods are disclosed for the therapeutic use of an *atonal*-associated nucleic acid or amino acid sequence. Also, an animal heterozygous for an *atonal*-associated gene inactivation is also disclosed having at least one *atonal*-associated nucleic acid sequence replaced by insertion of a heterologous nucleic acid sequence used to detect expression driven by an *atonal*-associated promoter sequence, wherein the inactivation of the *atonal*-associated nucleic acid sequence prevents expression of the *atonal*-associated nucleic acid.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/73764 A2

(51) International Patent Classification[7]: G01N

(21) International Application Number: PCT/US00/15410

(22) International Filing Date: 1 June 2000 (01.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/137,060 1 June 1999 (01.06.1999) US
60/176,993 19 January 2000 (19.01.2000) US

(71) Applicant *(for all designated States except US)*: **BAYLOR COLLEGE OF MEDICINE** [US/US]; One Baylor Plaza, Houston, TX 77030 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZOGHBI, Huda, Y.** [US/US]; 6618 Sewanee, Houston, TX 77005 (US). **BELLEN, Hugo** [US/US]; 3411 Mt. Vernon, Houston, TX 77006 (US). **BIRMINGHAM, Nessan** [US/US]; 5445 Braesvalley #708, Houston, TX 77096 (US). **HASSAN, Bassem** [US/US]; 1422 Richmond Avenue #3053, Houston, TX 77006 (US). **BEN-ARIE, Nissim** [IL/IL]; Department of Cell and Animal Biology, Alexander Silberman Institute of Life Sciences, Hebrew University of Jerusalem, Givat-Ram, 91904 Jerusalem (IL).

(74) Agent: **PAUL, Thomas, D.**; Fulbright & Jaworski, Suite 5100, 1301 McKinney, Houston, TX 77010 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/73764 A2

(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPEUTIC USE OF AN *ATONAL*-ASSOCIATED SEQUENCE FOR DEAFNESS, OSTEOARTHRITIS, AND ABNORMAL CELL PROLIFERATION

(57) Abstract: Compositions and methods are disclosed for the therapeutic use of an *atonal*-associated nucleic acid or amino acid sequence. Also, an animal heterozygous for an *atonal*-associated gene inactivation is also disclosed having at least one *atonal*-associated nucleic acid sequence replaced by insertion of a heterologous nucleic acid sequence used to detect expression driven by an *atonal*-associated promoter sequence, wherein the inactivation of the *atonal*-associated nucleic acid sequence prevents expression of the *atonal*-associated nucleic acid.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P01899WO0	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/15410	International filing date *(day/month/year)* 01 JUNE 2000	Priority date *(day/month/year)* 01 JUNE 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant BAYLOR COLLEGE OF MEDICINE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 DECEMBER 2000	26 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL C. WILSON Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/15410

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-121, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
pages 122-127, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
pages 1-14, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets~~/fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	2, 4, 8, 9, and 11-46	YES
	Claims	1, 3, 5-7, 10	NO
Inventive Step (IS)	Claims	2, 4, 8, 9, and 11-46	YES
	Claims	1, 3, 5-7, 10	NO
Industrial Applicability (IA)	Claims	1-46	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1, 3, 5-7, and 10 lack novelty under PCT Article 33(2) as being anticipated by Ben-Arie et al. (Nature).

Ben-Arie et al. teach transgenic mice lacking one or both alleles of an atonal-associated nucleic acid sequence (MATH 1) . The transgenic mice were generated by homologous recombination protocols using a vector comprising a nucleic acid sequence encoding a reporter gene flanked by an atonal-associated nucleic acid sequence. The mice lack the external germinal layer and lack foliation of the cerebellum. In addition, the mice have a reduction in cerebellum size.

Claims 2, 4, 8, 9 and 11-46 meet the criteria set out in PCT Article 33(2)-(3) since the prior art does not teach or fairly suggest the claimed invention.

Claims 1-46 meet the criteria set out in PCT Article 33(4), because the transgenic animals are useful in studying the phenotypic effects of alterations in proneural gene expression during development.

---------- NEW CITATIONS ----------
NONE

VIII. Certain observations on the internati nal application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to contain an adequate written description of the claimed transgenic animals and compositions. The description is inadequate because: the description fails to provide information regarding vector construct design for generating all of the transgenic animals and compositions encompassed in the claims.

Claims 1-46 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because: the description does not provide sufficient guidance to make all of the transgenic animals encompassed in the claims. As such, the description does not provide sufficient guidance to use the transgenic animals in the claimed screening methods. In addition, the description does not provide sufficient guidance to make and use the compositions for the claimed treatment methods as the description does not provide sufficient information with respect to how to target the proteins or nucleic acid sequences to specific cells or tissues, which cells or tissues to target, the level of protein or nucleic acid sequence needed for administration, the level of expression of the nucleic acid sequence required to effect a treatment. Furthermore, the state of the art teaches that providing proteins or nucleic acid sequences to treat disease conditions is unpredictable (see Sabate et al., Ledley, and Verma et al.).

Claims 1-46 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A61K 38/00; C07H 21/04; C07K 14/00, 14/46, 14/435; G01N 33/00; C12N 15/00, 15/09, 15/12, 15/63, 15/67, 15/85, 15/86, 15/87, 15/88 and US Cl.: 435/320.1, 455, 456, 458; 514/2, 44; 530/350; 536/23.1, 23.5, 24.1; 800/3, 9, 13

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P01899WO0	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/15410	International filing date *(day/month/year)* 01 JUNE 2000	Priority date *(day/month/year)* 01 JUNE 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant BAYLOR COLLEGE OF MEDICINE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 DECEMBER 2000	26 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL C. WILSON Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/15410

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-121 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 122-127 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages 1-14 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	2, 4, 8, 9, and 11-46	YES
	Claims	1, 3, 5-7, 10	NO
Inventive Step (IS)	Claims	2, 4, 8, 9, and 11-46	YES
	Claims	1, 3, 5-7, 10	NO
Industrial Applicability (IA)	Claims	1-46	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1, 3, 5-7, and 10 lack novelty under PCT Article 33(2) as being anticipated by Ben-Arie et al. (Nature).

Ben-Arie et al. teach transgenic mice lacking one or both alleles of an atonal-associated nucleic acid sequence (MATH 1) . The transgenic mice were generated by homologous recombination protocols using a vector comprising a nucleic acid sequence encoding a reporter gene flanked by an atonal-associated nucleic acid sequence. The mice lack the external germinal layer and lack foliation of the cerebellum. In addition, the mice have a reduction in cerebellum size.

Claims 2, 4, 8, 9 and 11-46 meet the criteria set out in PCT Article 33(2)-(3) since the prior art does not teach or fairly suggest the claimed invention.

Claims 1-46 meet the criteria set out in PCT Article 33(4), because the transgenic animals are useful in studying the phenotypic effects of alterations in proneural gene expression during development.

---------- NEW CITATIONS ----------

NONE

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to contain an adequate written description of the claimed transgenic animals and compositions. The description is inadequate because: the description fails to provide information regarding vector construct design for generating all of the transgenic animals and compositions encompassed in the claims.

Claims 1-46 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because: the description does not provide sufficient guidance to make all of the transgenic animals encompassed in the claims. As such, the description does not provide sufficient guidance to use the transgenic animals in the claimed screening methods. In addition, the description does not provide sufficient guidance to make and use the compositions for the claimed treatment methods as the description does not provide sufficient information with respect to how to target the proteins or nucleic acid sequences to specific cells or tissues, which cells or tissues to target, the level of protein or nucleic acid sequence needed for administration, the level of expression of the nucleic acid sequence required to effect a treatment. Furthermore, the state of the art teaches that providing proteins or nucleic acid sequences to treat disease conditions is unpredictable (see Sabate et al., Ledley, and Verma et al.).

Claims 1-46 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A61K 38/00; C07H 21/04; C07K 14/00, 14/46, 14/435; G01N 33/00; C12N 15/00, 15/09, 15/12, 15/63, 15/67, 15/85, 15/86, 15/87, 15/88 and US Cl.: 435/320.1, 455, 456, 458; 514/2, 44; 530/350; 536/23.1, 23.5, 24.1; 800/3, 9, 13

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: THOMAS D. PAUL
FULBRIGHT & JAWORSKI
1301 MCKINNEY, SUITE 5100
HOUSTON, TEXAS 77010

Received
SEP 05 2001

PCT

WRITTEN OPINION
(PCT Rule 66)

P01899WO0
Baylor
MLS

Date of Mailing *(day/month/year)*	29 AUG 2001
Applicant's or agent's file reference: P01899WO0	REPLY DUE within ONE months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15410	01 JUNE 2000	01 JUNE 1999

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant
BAYLOR COLLEGE OF MEDICINE

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [X] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 01 OCTOBER 2001

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer TERRY J. DEY JANET M. KERR PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/408 (cover sheet) (July 1998) ★

WRITTEN OPINION

International application No.
PCT/US00/15410

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-121, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the claims:
pages 122-127, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the drawings:
pages 1-14, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
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[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

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[X] the description, pages NONE

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[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanati ns supporting such statement

1. statement

Novelty (N)	Claims	2, 4, 8, 9, and 11-46	YES
	Claims	1, 3, 5-7, 10	NO
Inventive Step (IS)	Claims	2, 4, 8, 9, and 11-46	YES
	Claims	1, 3, 5-7, 10	NO
Industrial Applicability (IA)	Claims	1-46	YES
	Claims	NONE	NO

2. citations and explanations

Claims 1, 3, 5-7, and 10 lack novelty under PCT Article 33(2) as being anticipated by Ben-Arie et al. (Nature).

Ben-Arie et al. teach transgenic mice lacking one or both alleles of an atonal-associated nucleic acid sequence (MATH 1) . The transgenic mice were generated by homologous recombination protocols using a vector comprising a nucleic acid sequence encoding a reporter gene flanked by an atonal-associated nucleic acid sequence. The mice lack the external germinal layer and lack foliation of the cerebellum. In addition, the mice have a reduction in cerebellum size.

Claims 2, 4, 8, 9 and 11-46 meet the criteria set out in PCT Article 33(2)-(3) since the prior art does not teach or fairly suggest the claimed invention.

Claims 1-46 meet the criteria set out in PCT Article 33(4), because the transgenic animals are useful in studying the phenotypic effects of alterations in proneural gene expression during development.

---------- NEW CITATIONS ----------
NONE

VIII. Certain bservations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to contain an adequate written description of the claimed transgenic animals and compositions. The description is inadequate because: the description fails to provide information regarding vector construct design for generating all of the transgenic animals and compositions encompassed in the claims.

Claims 1-46 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.

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Claims 1-46 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): A61K 38/00; C07H 21/04; C07K 14/00, 14/46, 14/435; G01N 33/00; C12N 15/00, 15/09, 15/12, 15/63, 15/67, 15/85, 15/86, 15/87, 15/88 and US Cl.: 435/320.1, 455, 456, 458; 514/2, 44; 530/350; 536/23.1, 23.5, 24.1; 800/3, 9, 13